SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, a division of Janssen Pharmaceutica N.V. NAME OF FINISHED PRODUCT: To be determined NAME OF ACTIVE INGREDIENT: R076477	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: R076477-P01-103 CR004276 **Title of Study:** Plasma Concentrations, Metabolism and Excretion of ^{14}C-Paliperidone After a Single Oral Dose in Healthy Male Subjects		
Investigator: S. De Bruyn, M.D. – Stuivenberg Hospital, Antwerp; Belgium		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 7 July 2003 – 23 July 2003 Sample Analysis: 14 August 2003 – 25 August 2003		**Phase of development:** 1
Objectives: To investigate the metabolic pathways of paliperidone and excretion of paliperidone and its metabolites in healthy adult male subjects, both CYP2D6 poor and extensive metabolizers , after administration of a single 1-mg oral dose of ^{14}C-paliperidone. In addition, to evaluate the safety and tolerability of paliperidone, as well as the relationship between genotypes (CYP2D6, CYP3A4, CYP3A5, UGT1A1, and UGT1A6) and exposure to paliperidone and its metabolites.		
Methodology: Single-center, single-dose, open-label study of the absorption, metabolism, and excretion (AME) of paliperidone in healthy men (3 extensive and 3 poor metabolizers based on CYP2D6 phenotype). Eligible subjects were admitted to the study center the evening before study drug administration and remained at the study center until 168 hours after dosing (or longer if required up to a maximum of 14 days). Each subject received a single oral dose of ^{14}C-paliperidone with total radioactivity below 1000 µSv (16 µCi). Blood samples for plasma pharmacokinetic profile were obtained immediately before study drug administration and 0.5, 1, 1.5, 3, 6, 12, 16, 36, 48, 72, 96, 120, 144 and 168 hours postdose. Blood samples were obtained 2, 4, 8 and 24 hours postdose for determination of ^{14}C in whole blood. Samples for determination of serum creatinine were obtained 2, 4, 8 and 24 hours postdose. Urine was collected immediately prior to drug administration and from 0-4, 4-8, 8-12, 12-16, 16-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours after study drug administration. Fecal samples were collected per each stool, once before study drug administration and in the period from 0-168 hours after study drug administration. Collections of urine and feces (per 24 hours) were to continue beyond 168 hours, to a maximum of 336 hours (Day 15) for subjects who excrete radioactivity slowly (2 latest 24-hour urine collections each ≥2% of total radioactive dose) or have <7 feces stool samples over the 0 to 168-hour period. ^{14}C radioactivity was measured in plasma, urine, and feces. Aliquots of the 0- through 24-hour urine collections were analyzed for creatinine. Plasma concentrations of paliperidone and risperidone were determined by means of a validated LC-MS/MS method. The ^{14}C-labeled moiety in plasma and urine was determined by liquid scintillation counting. For all plasma samples, the lower limits of quantification for paliperidone and risperidone were 0.100 ng/mL. For all plasma and urine samples the lower limits of quantification for ^{14}C-paliperidone was 72 dpm/mL (=2.0n g-eq/mL).		
Number of Subjects (planned and analyzed): Six healthy men, 3 extensive and 3 poor metabolizers based on CYP2D6 phenotype, were to participate in the study. Five subjects, 3 extensive and 2 poor metabolizers, received a single dose of ^{14}C-paliperidone, completed the study (i.e., completed all assessments through Day 8) and were considered evaluable for safety (the Safety Analysis Set), as well as for pharmacokinetics.		
Diagnosis and Main Criteria for Inclusion: Subjects were healthy white men between the ages of 40 and 60 years. Subjects were healthy based on medical history, physical examination, clinical laboratory evaluation, and electrocardiogram. Dextromethorphan metabolic ratio of >0.345 (poor metabolizer) or <0.0255 (extensive metabolizer). Body Mass Index (BMI): (weight [kg]/height [m^2]) between 20 and 28 kg/m2, inclusive.		
Test Product, Dose and Mode of Administration, Batch No.: Single oral 0.988-mg dose of ^{14}C-paliperidone, oral solution (aqueous formulation at a final concentration of 0.0984 mg/mL). Batch No.: unlabeled paliperidone oral solution: ZR076477EIA031 (manufacturing date: 23 April 2003, retest date: 23 October 2004): ^{14}C-paliperidone: 1763 (expiration date: not applicable)		
Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable		

SYNOPSIS (CONTINUED)

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Duration of Treatment: Single oral dose

Criteria for Evaluation:

Pharmacokinetics: Plasma paliperidone, ^{14}C radioactivity, and metabolite profiles were determined. Plasma C_{max}, t_{max}, AUC_{last}, AUC_{24}, AUC_{∞}, λ_z, $t_{1/2term}$, CL/F of ^{14}C and paliperidone were estimated by non-compartmental analysis. Based on the individual urine excretion data and on the serum creatinine concentrations, Ae, Ae,%dose, CL_R, $CL_{R,24h}$,and CL_{cr} of ^{14}C and paliperidone and CL_{GFR} and CL_{act} of paliperidone were estimated. The excretion half-life of ^{14}C in urine was also estimated based on excretion rate-time profiles.

Safety: Evaluation was based of the incidence, type, and severity of all treatment-emergent adverse events, and on change from screening to the end of the study in clinical laboratory results, vital sign measurements, and postural changes in blood pressure and heart rate.

Statistical Methods:

Pharmacokinetics: Plasma concentrations of ^{14}C and paliperidone, as well as estimates of pharmacokinetic parameters were listed and graphically presented, and the excretion analysis of total radioactivity in plasma, urine and feces was summarized. Descriptive statistics were calculated, including summaries by CYP2D6 phenotype.

Safety: The number of subjects with adverse events was summarized. Summary statistics were calculated for clinical laboratory values. Other safety data were listed by individual subject. Changes in blood pressure and heart rate measurements were also presented graphically.

SUMMARY – CONCLUSIONS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS: Five white men, 3 extensive metabolizers and 2 poor metabolizers, received study medication and completed the study. The ages ranged from 40 to 63 years (mean: 51.2 years), the body weights ranged from 68.7 to 78.6 kg (mean: 73.38 kg), and BMI ranged from 24 to 28 kg/m^2 (mean: 25.5 kg/m^2).

PHARMACOKINETIC RESULTS:

Pharmacokinetics of Total Radioactivity (TR) and paliperidone (UD) in plasma:

The mean (SD) pharmacokinetic parameters of TR and UD after administration of a single oral dose of ^{14}C-paliperidone are summarized in Table A.

Table A: Plasma Pharmacokinetic Parameters of ^{14}C-Labeled Moiety and Unchanged Paliperidone (Mean ± SD) After a Single Dose of 1-mg ^{14}C-paliperidone [Source: Attachment 1.4]

	All (N=5)			EM (N=3)			PM (N=2)		
^{14}C-Labeled Moiety (TR)									
C_{max}, ng-equivalent/mL	9.54	±	1.35	9.40	±	1.73	9.75	±	1.06
t_{max}, h	1.40	±	0.224	1.50	±	0.00	1.25	±	0.354
AUC_{24}, ng-eq·h/mL	114	±	19.9	116	±	27.3	112	±	7.78
AUC_{∞}, ng-eq·h/mL	175	±	30.7	179	±	41.9	168	±	9.90
$t_{1/2term}$, h	15.2	±	2.15	15.4	±	1.35	14.9	±	3.82
CL/F, mL/min	97.9	±	17.6	96.8	±	24.4	99.6	±	6.22
Unchanged Paliperidone (UD)									
C_{max}, ng/mL	8.85	±	1.31	8.59	±	1.79	9.24	±	0.00707
t_{max}, h	1.30	±	0.274	1.33	±	0.289	1.25	±	0.354
AUC_{24}, ng·h/mL	111	±	22.0	113	±	30.1	109	±	9.90
AUC_{∞}, ng·h/mL	187	±	29.3	190	±	38.4	182	±	19.8
$t_{1/2term}$, h	24.8	±	4.35	24.1	±	4.49	26.0	±	5.59
CL/F, mL/min	91.0	±	15.0	90.3	±	20.0	92.1	±	10.0
Ratio AUC_{24}: UD/TR	0.970	±	0.0250	0.965	±	0.0311	0.977	±	0.0205

EM: extensive metabolizer; PM: poor metabolizer

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PHARMACOKINETIC RESULTS (continued): In the overall population, average peak plasma concentration of TR (9.54 ng-eq/mL) was attained 1.40 hours after dosing. Average peak plasma concentration of UD (8.85 ng/mL) was reached after 1.30 hours. The terminal half-life of TR and UD was on average 15.2 hours and 24.8 hours, respectively. This difference was probably caused by a higher LLOQ for TR compared to UD. AUC_{∞}-values of TR averaged 175 ng-eq.h/mL, those of UD were 187 ng.h/mL. At 24 hours after dosing, the percentage of UD versus TR in plasma is on average 97.0%. No differences are found between CYP2D6 extensive and poor metabolizers.

Excretion in Urine and Feces:
At 7 days after a single oral dose of ^{14}C-paliperidone, 91% of the administered radioactivity has been excreted as ^{14}C-labeled moiety. The cumulative excretion of the TR amounted to 80% in the urine (Table B) and 11% in the feces. There were no differences between extensive and poor metabolizers in urinary excretion (% of the dose) of ^{14}C-labeled moiety. Furthermore no discrimination could be made between extensive (13%) and poor (8%) metabolizers for excretion of ^{14}C-labeled moiety in feces.

Table B: Clearance and Urine Parameters of ^{14}C-Labeled Moiety (Mean ± SD) After a Single Dose of 1-mg ^{14}C paliperidone

	All (N=5)			EM (N=3)			PM (N=2)		
^{14}C-Labeled Moiety									
Ae, % dose	79.6	±	4.20	77.6	±	0.775	82.7	±	6.15
CL_R, mL/min	76.8	±	13.6	74.1	±	18.5	80.8	±	1.20
CL_{CR}, mL/min	113	±	10.3	108	±	7.37	121	±	10.5
Unchanged Paliperidone									
Ae, % dose	59.4	±	7.12	55.7	±	6.66	64.9	±	3.68
CL_R, mL/min	53.1	±	9.47	49.2	±	8.59	59.1	±	9.69

EM: extensive metabolizer; PM: poor metabolizer

SAFETY RESULTS: Two of the 5 subjects who received study medication experienced treatment-emergent adverse events: moderately severe postural hypotension and syncope in 1 subject and mild allergic reaction (described as infraorbital swelling probably due to an allergic reaction, and considered doubtfully related to the study medication) and asthenia in the second subject. With the exception of allergic reaction which was persisting at the end of the study, the adverse events resolved without treatment intervention. There were no deaths, no serious adverse events, and no subject discontinued from the study due to an adverse event.

There were no clinically relevant changes in laboratory test results. With the exception of postural hypotension which was reported as an adverse event in 1 subject, there were no clinically relevant changes in vital sign measurements.

CONCLUSION: The unchanged drug paliperidone accounted for a large part of the total radioactivity in plasma. The percentage of UD versus TR in plasma is on average 97%. There were no differences in paliperidone pharmacokinetic parameters observed between CYP2D6 extensive and poor metabolizers. No effect of genotype was observed for CYP2D6, UGT1A1 or UGT1A6 on the plasma exposure of TR and UD.

Seven days after administration of a single oral dose of 1 mg ^{14}C-paliperidone to 5 healthy male subjects, 91% of the dose was excreted in urine and feces as ^{14}C-labeled moiety. The cumulative excretion of the TR amounted to 80% in the urine and 11% in the feces. The cumulative urinary excretion of unchanged paliperidone amounted to 59%. About 50% of the UD is excreted by means of filtration, the other half of UD is cleared renally by active processes.

The administration of a single oral 1-mg dose of ^{14}C-paliperidone as an oral solution was safe and well tolerated in healthy men.

Date of the report: 27 January 2004

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